AF/1641

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PTO/SB/21 (08-00)
Approved for use through 10/31/2002. OMB 0651-0031
Patent and Trademark Office: U.S. DEPARTMENT OF COMMERCE

TRANSMITTAL FORM

(to be used for all correspondence after initial filing)

Application	08/286,189
Filing Date	August 5, 1994
First Named	Sonia E. Sanhueza
Group Art Unit	1641
Examiner Name	J. Parkin
Total Number of Pages in This Submission: 75	Attorney Docket Number: 1038-384 MIS:jb

ENCLOSURES *(check all that apply)*

- [X] Fee Transmittal Form
  - [X] Fee Attached
- [ ] Amendment / Response
  - [ ] After Final
  - [ ] Affidavits/declaration(s)
- [X] Extension of Time Request
- [ ] Express Abandonment Request
- [ ] Information Disclosure Statement
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- [ ] Response to Missing Parts/ Incomplete Application
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- [ ] Assignment Papers *(for an Application)*
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- [ ] Petition
- [ ] Petition to Convert a Provisional Application
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- [ ] After Allowance Communication to Group
- [ ] Appeal Communication to Board of Appeals and Interferences
- [X] Appeal Communication to Group *(Appeal Notice, Brief, Reply Brief)*
- [ ] Proprietary Information
- [ ] Status Letter
- [X] Other Enclosure(s) *(please identify below)*:
  - **(1) Appendix - Claims Appealed**
  - **(2) Declaration of Prof. Prince**
  - **(3) Postcard**

Remarks

SIGNATURE OF APPLICANT, ATTORNEY, OR AGENT

Firm or Individual name	**Michael I. Stewart (Reg. No. 24,973)**
Signature	
Date	**February 27, 2002**

CERTIFICATE OF MAILING

I hereby certify that this correspondence is being deposited with the United States Postal Service with sufficient postage as first class mail in an envelope addressed to: Commissioner for Patents, Washington, D.C. 20231 on this date: [ ]

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(1)

#34 Appeal brief (3)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	08/286,189
Appl'n. No.	:	Sonia E. Sanhueza
Filed	:	August 5, 1994
Title	:	INACTIVATED RESPIRATORY SYNCYTIAL VIRAL VACCINES
Grp./A.U.	:	1641
Examiner	:	J. Parkin
Docket No.	:	1038-384 MIS:jb
Date	:	February 27, 2002

BY COURIER

The Commissioner of Patents
and Trademarks,
Box AF
Washington, D.C. 20231,
U.S.A.

APPEAL BRIEF

Dear Sir:

1. Introduction

This Appeal Brief is submitted in respect of the appeal from the Final Rejection of claims 1, 3 to 9 and 11 to 16. The enclosed cheque includes the Appeal Brief fee.

2. Extension of Time

Petition is hereby made under the provisions of 37 CFR 1.136(a) for an extension of three months of the period for filing an Appeal Brief. Our enclosed cheque includes the prescribed fee.

3. Real Party in Interest

The real party of interest in this appeal is Connaught Laboratories Limited by virtue of a deed of Assignment from the inventors recorded under Reel/Frame 7150/0232.

4. Related Appeals and Interferences

Applications Nos. 08/472,174 filed June 7, 1995 and 08/583,124 filed June 28, 1996, assigned to the assignee, also are on appeal. A decision by the Board of Appeals and Patent Interferences in either of those appeals may directly affect or be directed affected by or have a bearing on the Board's decision in the pending appeal. The appellant, the appellant's legal representative, and assignee are unaware of any other such appeals or interferences

5. Status of Claims

The application was filed with 19 claims. Claims 17 to 19 were withdrawn from consideration as being directed to a non-elected invention. Claims 1 and 5 have been amended. Claims 2 and 10 have been cancelled. Claims 12 and 14, originally dependent claims, were rewritten as independent claims. The claims on appeal appear in the Appendix hereto.

6. Status of Amendments

No Amendment subsequent to final action has been filed.

7. Summary of Invention

The present invention relates to immunology and, in particular, the provision of a vaccine against infection caused by respiratory syncytial virus. The invention involves a vaccine composition capable of producing a respiratory syncytial (RS) virus specific protective immune response in a human host immunized therewith, comprising a purified inactivated RS viral preparation which is free from cellular and serum components and which is non-infectious, non-immunopotentiating, immunogenic and protective, and a carrier therefor (page 5, lines 13 to 28; claims 1, 3 and 4). An inactivated RS viral vaccine composition which is protective and non-immunopotentiating has not previously been described.

The invention further includes a method of preparing a non-immunopotentiating, vaccine composition capable of protecting a human host

immunized therewith against disease caused by infection by respiratory syncytial (RS) virus, comprising a plurality of steps. The RS virus is grown on a continuous cell line of vaccine quality. The grown virus is harvested and the harvested virus is purified under non-denaturing conditions to produce a purified virus free from cellular and serum components. The purified virus then is inactivated with an inactivating agent to provide a non-infectious, non-immunopotentiating and protective RS viral preparation, which then is formulated as a vaccine (page 4, lines 20 to 32; claims 5 to 9, and 11 to 14). In this procedure, the RS virus first is purified and then inactivated. This order of steps is the key to providing a non-immunopotentiating composition.

The invention additionally includes a method of immunizing a host against disease caused by respiratory syncytial virus by administering to the host an effective amount of the vaccine composition. (page 5, line 29 to page 6, line 1; claims 15, 16).

8. Issues for Consideration

The sole issue for consideration is:

- rejection of claims 1, 3 to 9 and 11 to 16 under 35 USC 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

9. Grouping of Claims

The claims stand or fall together, having regard to the nature of the rejection.

10. Argument

(a) Background

Human respiratory syncytial (RS) virus is the main cause of lower respiratory tract infections among infants and young children. Globally, 65 million infections occur every year resulting in 160,000 deaths. In the USA alone, 100,000 children may require hospitalization for pneumonia and bronchiolitis caused by RS

virus in a single year. Providing inpatient and ambulatory care for children with RS virus infections costs in excess of $340 million annually in the USA. Severe lower respiratory tract disease due to RS virus infection predominantly occurs in infants two to six months of age. Approximately 4,000 infants in the USA die each year from complications arising from severe respiratory tract disease caused by infection with RS virus and Parainfluenza type 3 virus (PIV-3). The World Health Organization (WHO) and the National Institute of Allergy and Infectious Disease (NIAID) vaccine advisory committees have ranked RS virus second only to HIV for vaccine development.

RS virus is a member of the *Paramyxoviridae* family of the pneumovirus genus. The two major protective antigens are the envelope fusion (F) and attachment (G) glycoproteins. The F protein is synthesized as a 68 kDa precursor molecule (FO) which is proteolytically cleaved into disulfide-linked Fl (48 kDa) and F2 (2O kDa) polypeptide fragments. The G protein (33 kDa) is heavily O-glycosylated giving rise to a glycoprotein of apparent molecular weight of 90 kDa. Two broad subtypes of RS virus have been defined: A and B. The major antigenic differences between these subtypes are found in the G glycoprotein.

A safe and effective RS virus vaccine is not available and is urgently needed. Approaches to the development of RS virus vaccines have included inactivation of the virus with formaldehyde, isolation of cold-adapted and/or temperature-sensitive mutant viruses and isolation of the protective antigens of the virus. Clinical trial results have shown that both live attenuated and formalin-inactivated vaccines failed to adequately protect vaccinees against RS virus infection. Problems encountered with cold-adapted and/or temperature-sensitive RS virus mutants administered intranasally included clinical morbidity, genetic instability and overattenuation.

A live RS virus vaccine administered subcutaneously also was not efficacious. Inactivated RS viral vaccines have typically been prepared using formaldehyde as the inactivating agent. Data has been reported on the immune response in infants and children immunized with formalin-inactivated RS virus. Infants (2 to 6 months of age) developed a high titre of antibodies to the F glycoprotein but

had a poor response to the G protein. Older individuals (7 to 40 months of age) developed titres of F and G antibodies comparable to those in children who were infected with RS virus. However, both infants and children developed a lower level of neutralizing antibodies than did individuals of comparable age with natural RS virus infections. The unbalanced immune response, with high titres of antibodies to the main immunogenic RS virus proteins F (fusion) and G (attachment) proteins but a low neutralizing antibody titre, may be in part due to alterations of important epitopes in the F and G glycoproteins by the formalin treatment.

Furthermore, some infants who received the formalin-inactivated RS virus vaccine developed a more serious lower respiratory tract disease following subsequent exposure to natural RS virus than did non-immunized individuals. The formalin-inactivated RS virus vaccines, therefore, have been deemed unacceptable for human use.

Evidence of an aberrant immune response also was seen in cotton rats immunized with formalin-inactivated RS virus. Furthermore, evaluation of RS virus formalin-inactivated vaccine in cotton rats also showed that upon live virus challenge, immunized animals developed enhanced pulmonary histopathology.

The mechanism of disease potentiation caused by formalin-inactivated RS virus vaccine preparations remains to be defined but is a major obstacle in the development of an effective RS virus vaccine. The potentiation may be partly due to the action of formalin on the F and G glycoproteins. Additionally, a non-RS virus specific mechanism of disease potentiation has been suggested, in which an immunological response to contaminating cellular or serum components present in the vaccine preparation could contribute, in part, to the exacerbated disease. Indeed, mice and cotton rats vaccinated with a lysate of HEp-2 cells and challenged with RS virus grown on HEp-2 cells developed a heightened pulmonary inflammatory response.

Furthermore, RS virus glycoproteins purified by immunoaffinity chromatography using elution at acid pH were immunogenic and protective but also induced immunopotentiation in cotton rats.

There clearly remains a need for immunogenic preparations, including vaccines, which are not only effective in conferring protection against disease caused by RS virus but also does not produce unwanted side-effects, such as immunopotentiation.

(b) Nature of the Invention

The applicants have found that, if the virus first is purified and then inactivated using β-propiolactone, ascorbic acid or octyl glycopyranoside, then a safe and effective vaccine preparation can be obtained which, in particular, elicits a protective immune response without causing enhanced pulmonary pathology (immunopotentiation).

Applicants present independent claim 1 to the vaccine, independent claims 5, 12 and 14 directed to the method and independent claim 15 to a method of immunizing. It is submitted that this procedure, the vaccine formed thereby and the method of immunization using the vaccines as defined by applicants claims are fully enabled by the specification.

(c) Rejection under 35 USC 112, first paragraph

As noted by the Examiner in the Office Action of September 27, 1999, the disclosure of this application claims the preparation of a protective vaccine composition comprising purified and inactivated respiratory syncytial viruses (RSVs) of the subtype A. Virus was prepared from infected vaccine quality VERO cells, concentrated by ultracentrifugation, purified by sucrose density gradient centrifugation, gel filtration and chromatography, and inactivated by n-octyl-β-D-glucopyranoside treatment. These compositions were used to immunize cotton rats and their immunogenicity and pathogenicity examined. The inactivated RSV preparations elicited protective immune responses in the cotton rats without causing the exacerbated pulmonary pathology associated with other putative vaccine compositions.

The substance of the Examiner's basis for rejection appears to be that the cotton rat, in which applicants data was generated, is not an art-recognized animal model for assuring the efficacy of a protective human RSV vaccine.

It had previously been pointed out that Coe et al, if record herein, states:

> "Pulmonary pathology produced in cotton rats by these pathogens [including RSV] is similar to that seen in humans. Recent clinical studies with RSV have shown a high level of correlation between experimental results in cotton rats and outcome in clinical trials" (emphasis added)

As was pointed out, the article cites the Groothuis et al reference of record herein as authority for this statement.

In the Final Action, the Examiner states:

> "Contrary to applicants assertion, the Coe et al (1996) teaching fails to enable the claimed invention".

In this regard, the Examiner states:

> "First, this teaching fails to provide any evidence pertaining to the suitability of the cotton rat model for predicting immune response in humans. Second, while reference was made to other published studies, none of the relevant facts were provided from those studies in this publication. Descriptions of the immunogen employed and immune parameters examined were not provided."

Since the reference referred to by Coe et al (Groothuis et al) is of record herein and applicants had referred to this paper earlier in their submission, it would not seem necessary to specify the immunogen, which was an RSV immunoglobulin.

The Examiner further states in the Final Action that:

> "Applicants are advised that the presentation of more appropriate publications or other suitable evidence providing reproducible data derived from the cotton rat model might obviate the rejection."

Responding to this invitation, applicants submit herewith a Declaration under 37 CFR 1.132 of Professor Gregory A. Prince*, along with the Exhibits attached thereto. From Professor Prince's background and published literature (see para 1 and Exhibit I), it is evident he is an expert in the field of RSV and a person whose opinion is to be respected.

In paragraphs 3.1 and 3.2, Professor Prince describes the biomedical uses of the cotton rat as a relevant model of many human diseases. In paragraphs 4.1, 4.2, 4.3 and 4.4, Professor Prince describes the steps taken towards licensure of two RSV prophylactic drugs. Prince et al (Exhibit III) first showed in cotton rats that anti-RSV immunoglobulin was able to protect against RSV disease. As seen in Exhibit III, quantitative studies showed that cotton rats could be protected from pulmonary infection if plasma RSV neutralizing antibody titers of 1:350 or greater were achieved and that there was no evidence of disease exacerbation.

On the strength of this cotton rat data, NIH proposed funding of a clinical trial of RSV prophylaxis in high risk infants using immunoglobulin. This clinical trial was carried out by a team led by Dr. Val Hemming. Using as a target, the very titer of anti-RSV antibody shown to be protective in cotton rats, successful clinical trials of passive IgG prophylaxis of RSV disease were conducted in high risk infants, the results being reported in Groothuis et al, the basis of the statement by Coe et al referred to above. The results of the trial led to licensure of the first RSV prophylaxis drug, RespiGam.

As Professor Prince emphasizes, in this and subsequent immunoglobulin studies, the FDA was sufficiently confident of the results of the cotton rat experiments that they allowed progression to human clinical trials without requiring testing in non-human primate. In paragraph 4.3, Professor Prince refers to a further study in which therapeutic human trials confirmed what the cotton rat had shown, namely that immunoglobulin reduced viral titers. As Professor Prince notes in paragraph 4.4, the cotton rat model has been used as a successful model in predicting the efficacy of an antiviral compound, Ribavirin, against RSV infection.

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* Unsigned copy enclosed. Signed copy to follow.

Having regard to the opinion expressed by Professor Prince in paragraph 6 of the Declaration, it is submitted that the cotton rat model is a model of RSV infection in humans. In addition, it is noted that the same opinion is expressed by Murphy et al in WO 93/21300, also of record herein, where, after reviewing the literature on pages 9 and 10, including some of the references referred to above, they conclude:

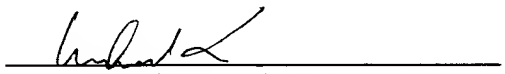
> ".... based on these studies, it would appear that the cotton rat constitutes a relevant model for predicting the success of a RSV vaccine in infants and small children" (page 10, lines 16 to 18)"

Having regard thereto, it is submitted that the Examiner is in error and the claims are fully enabled by the disclosure. Hence the rejection of claims 1, 3 to 9 and 11 to 16 under 35 USC 112, first paragraph, should not be sustained.

11. Summary

Having regard to the above, it is submitted that the rejection of claims 1, 3 to 9 and 11 to 16 under 35 USC 112, first paragraph, should be REVERSED.

Respectfully submitted,



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